

## Histopathological Characteristics of Explanted Human Prosthetic Arterial Grafts: Implications for the Prevention and Management of Graft Infection

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**Objective:** to study the histopathological characteristics of prosthetic vascular graft infection.

**Design:** prospective clinical study over 2 years.

**Setting:** University Hospital.

**Materials:** 36 infected and 29 uninfected (control) chronically implanted vascular prostheses (half aortic) were removed and 352 sections prepared.

**Chief outcome measures:** light microscopy (multiple stains), scanning electron microscopy (SEM), and multiple culture techniques to identify characteristics of healing, infection, and microorganisms.

**Main results:** Acute inflammation (AI) (neutrophils, granulocytes and necrosis) were seen in 75% of infected grafts, were most prominent in the perigraft tissue and rarely seen on the luminal surface. These were usually well localised, leaving the remainder of a graft well incorporated with no signs of infection. In 25% of clinically infected, culture-positive grafts there was no significant acute inflammation. Chronic inflammation (CI) (macrophages, lymphocytes, monocytes, giant cells) was seen in 70% of both control and infected grafts. In 50% of both groups a significant lymphocytic population was composed exclusively of T-lymphocytes suggesting a true host vs. graft response. Unincorporated chronically implanted grafts (>1 yr) were seen with equal frequency in the two groups although more diffusely unincorporated grafts were infected. Microorganisms were cultured from 23 infected grafts (64%) and were, at microscopy, mostly found outside the graft and nerves on the luminal side.

**Conclusions:** This data cast doubt on criteria commonly used to distinguish graft infections and host vs. graft reactions from normal graft healing. Acute and chronic inflammation are not predictive of infection.

**Key Words:** Histopathology; Infection; Prosthetic arterial grafts.

### Introduction

Prosthetic vascular grafts have revolutionised the surgical treatment of occlusive and aneurysmal disease in the last three decades. Despite their enviable record, a spectrum of healing complications has been evident since the first human use of these grafts. These complications include acute and chronic perigraft infection, seroma formation, anastomotic failure, and prosthetic-enteric erosion. They occur in 1–6% of patients following successful graft implantation,<sup>1–3</sup> pose a serious threat to the life and limbs of the

patient, and demand innovative treatment for their solution. Significant improvement in the surgical management of these problems has occurred over the last two decades, but understanding of their cause and clinical evolution remains limited. Although there have been a substantial number of experimental studies in non-human animals, there have been few human studies following prosthetic graft implantation that carefully evaluate the healing or incorporation process of the prosthetic implant itself. While the vascular surgeon has been concerned with improving the results of treatment for threatened patients, the lack of concerted efforts to define human prosthetic graft healing offer little hope of preventing these dreaded complications in the foreseeable future.

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## Materials and Methods

The present prospective study examines the histologic characteristics of human prosthetic arterial grafts from infected and non-infected explants. During a 2-year period, 1987–88, 65 consecutive explanted prostheses were studied prospectively by microbiological culture, and light and scanning electron microscopy. Thirty-six grafts (27 Dacron, seven PTFE, two Dacron/PTFE) were considered clinically infected when cultures of the graft were positive and/or the graft was poorly incorporated by fibrous tissue, and/or surrounded by fluid or pus. Twenty-nine grafts (16 Dacron, 12 PTFE, one Dacron/PTFE) served as controls being explanted for non-infectious reasons (23 thrombosis, six revisions for stenosis, pseudo- or anastomotic aneurysms). After explantation, each graft was immediately prepared for microbiological cultures and cut in a standardised fashion. A total of 249 sections of infected and 103 sections of control grafts were evaluated. Another 11 sections of infected and five sections of control grafts were excluded because of unsatisfactory preparation.

### *Light microscopy*

Representative sections of graft and surrounding tissue were fixed in formalin, embedded in paraffin, cut into 5 µm sections, and then stained with the following stains:

Hematoxylin-eosin (H & E) was used to evaluate the overall architecture of tissue, presence of acute and chronic inflammatory cells (neutrophils, lymphocytes, monocytes or macrophages, giant cells) perigraft necrosis, fibrin deposition or scarring (incorporation), and presence of fungal or clusters of bacterial organisms.

Trichrome (connective tissue stain) was used to determine the degree of fibrous incorporation.

Brown and Brenn (Gram stain) was used for the identification of Gram positive, Gram negative, and fungal organisms.

In addition, representative sections of fresh graft and surrounding tissues from selected cases were also fixed in paraformaldehyde, embedded in glycolmethacrylate, and then stained using PAP (immunohistochemical) technique with Leu-4 and Pan-B antisera to classify the lymphocyte population in the tissues into Type T and B types respectively.

The following classifications were used in this study:

Acute inflammation — the presence of neutrophils, granulocytes, and perigraft tissue necrosis defined acute inflammation.

Chronic inflammation — the presence of monocytes, macrophages, lymphocytes and giant cells indicated the presence of chronic inflammation and/or foreign body reaction.

Incorporation — incorporation was evaluated by determining the extent of collagenous scarring in the perigraft tissue and in the graft wall itself using both the H & E and trichrome stains. Fibrin deposition and necrosis indicated lack of incorporation while scar formation around the graft indicated the presence of incorporation.

The development of pseudointima (scar or clot lining the luminal side of the graft) was also noted.

### *Grading*

All specimens were examined blindly by the same pathologist and graded according to an arbitrary scale, 0–3. A double test of this grading system revealed less than 10% variability. Cellular infiltration was graded as follows: 0 = no inflammatory cell response; 1 = scattered, scant inflammatory cells; 2 = irregular spread clusters; 3 = sheets or extensive confluent infiltration.

#### Peri-graft Collagenisation

- 0 no collagen
- 1 scattered, scant collagen bands
- 2 small sheets to aggregates — discontinuous, thickness on outside smaller than that of graft
- 3 extensive scarring — continuous, thickness more than that of graft

#### Collagenisation in graft wall

- 0 no collagen
- 1 less than 30% of graft interstices
- 2 discontinuous, but more than 30%
- 3 extensive between all graft fibers

#### Pseudointima

- 0 no pseudointima
- 1 discontinuous, thickness less than 30% of graft wall
- 2 continuous, thickness less than 30% of graft wall

3 fully developed continuous when calculating the results only a grade >2 was considered as significant regarding all these parameters.

### Scanning Electron Microscopy (SEM)

The special preparation required for scanning electron microscopy was performed by an extensively trained technologist who was blinded regarding the category of the specimen. The purpose of using SEM was to document the presence of microorganisms and/or biofilm on the surface of the grafts. SEM was performed in two steps: first, the intact surface was scanned and secondly, the layers covering the graft surface were disrupted by instrumentation and then reexamined.

In order to increase the likelihood of culturing slime producing bacteria the specimens were mechanically disrupted by grinding and then inoculated on *Brucella* and thioglycolate broth plates and on blood/chocolate agar for growth of bacteria as well as fungi.

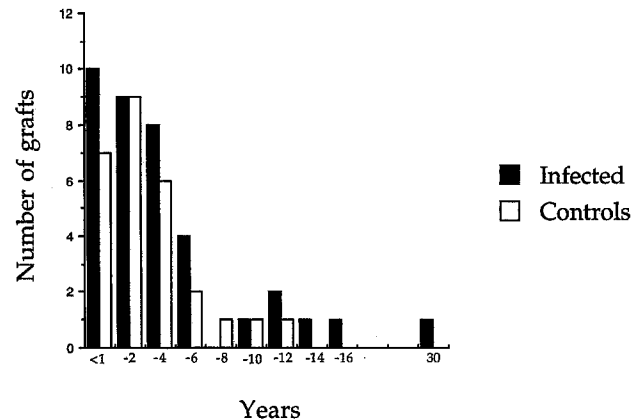
Statistical analysis used the Student's *t*-test, the Mann-Whitney U-test and  $\chi^2$  analysis.

## Results

**Table 1. Original implantation site of the explanted graft**

	Infected	Controls
Aorto-visceral	–	2
Aortic	–	1
AIBG	3	4
AFBG	18	7
Femoro-femoral	1	2
Femoro-popliteal	3	5
Axillo-femoral	8	–
Innominate/subclavian	1	2
AV fistula	2	6

As shown in Table 1, the original sites of the explanted grafts were similar in the two groups with approximately half of the grafts recovered from an aortic



**Fig. 1.** Distribution of implantation times for explanted vascular grafts.

location. Of the infected aortic grafts, 15 were primary graft infections and six were associated with aortoenteric fistulae. The mean implantation time of the infected grafts was 4 years, 2 months (range 1 mo–30 yrs) and 2 years, 9 months (range 1 mo–12 yrs) for the controls. The distribution of implantation times are shown in Fig. 1.

**Table 2. Distribution of acute inflammatory reaction and the presence of necrosis**

	Acute inflammation			Necrosis
	Perigraft tissue	Graft wall	Luminal surface	
Infected (n = 36)	13/36%	12/33%	8/22%	21/58%
Controls (n = 29)	3/10%	1/3%	0/0%	1/3%
<i>p</i>	0,003	0,004	0,01	<0,001

Acute inflammation (Table 2) as defined by neutrophils, granulocytes and/or necrosis occurred in 75% of the infected grafts leaving 25% of the infected grafts with no histologic signs of acute reaction or necrosis. Of these, 66% were positive for microorganisms by culture and microscopy. The degree of acute inflammation was significantly higher in the perigraft tissue than on the luminal surface ( $p < 0.001$ ). The acute inflammation and necrosis was very localised in some specimens with the remainder of the graft well incorporated and with no signs of infection. This is demonstrated by the fact that among individual sections of the infected grafts, 108 (43%) were graded 0 for acute inflammation/necrosis. These localised infections did not seem preferential in their locations, i.e. retroperitoneum *vs.* groins. As expected,

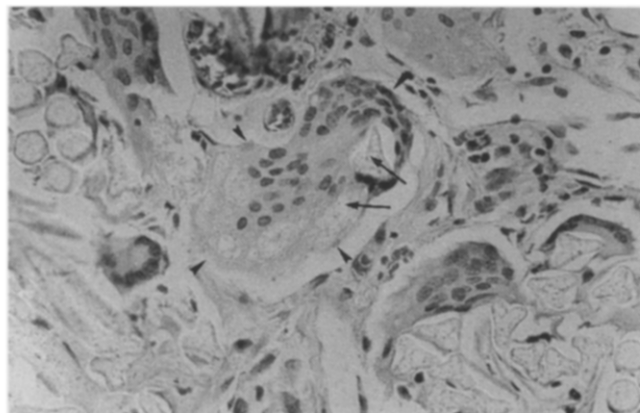
a comparison with the control grafts revealed significantly greater acute reaction around the infected grafts. Interestingly however, 14% of the non-infected (control) grafts also revealed signs of significant, perigraft acute inflammation or necrosis. Chronic

**Table 3. Chronic inflammation and foreign body reaction**

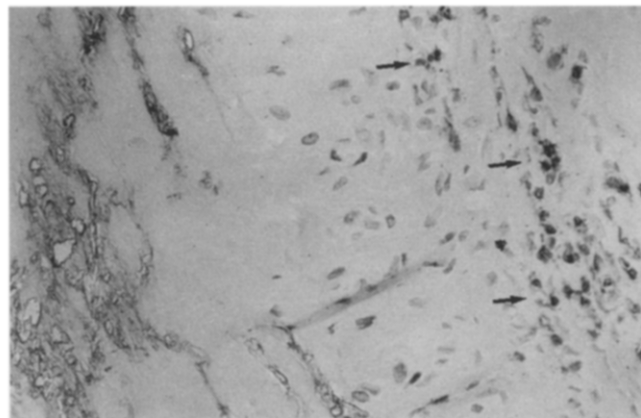
	Giant cells	Lymphocytes	Monocytes
Infected ( <i>n</i> = 36)	28/78%	19/53%	24/67%
Controls ( <i>n</i> = 29)	20/69%	14/48%	18/62%
<i>p</i>	0.06	0.9	0.9

inflammation (Table 3) as defined by monocyte and lymphocyte infiltration and the presence of macrophages and giant cells (the latter representing a foreign body reaction) was seen in the majority of, and in equal rates in, infected and control grafts (Fig. 2). Grafts with significant lymphocyte infiltration were subjected to special immunohistochemical staining (Leu 4, Pan B) to classify the lymphocytes. The lymphocyte population was in all instances almost exclusively made up of T-lymphocytes (Fig. 3) Seventy percent of all grafts showed significant histologic reaction in at least one of the parameters of chronic inflammation. Graft healing or incorporation (Table 4) as determined by fibrin deposition, collagenisation in the perigraft tissue and in the graft wall itself revealed no difference between infected and control grafts. However, the development of pseudointima was significantly better in the infected grafts.

The following subgroups were statistically com-



**Fig. 2.** Light microscopy (H & E stain) of a non infected Dacron graft explanted 3 years after implantation with a very strong chronic inflammatory/foreign body reaction with giant cell (arrowheads) engulfing graft material (arrow).



**Fig. 3.** Light microscopy (Leu-4, Pan-B) of an infected PTFE graft with mild-moderate chronic inflammation and T-lymphocyte infiltration (arrows).

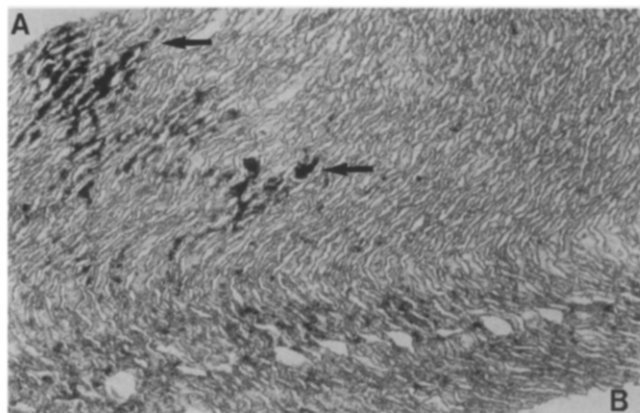
pared with no statistically significant differences being identified: positive *vs.* negative for the presence of microorganisms by culture and/or microscopy, implantation time (more *vs.* less than 2 years), and type of graft material (Dacron *vs.* PTFE). It is also noteworthy that obvious graft disruption was found in one of the infected grafts (Dacron) but in two of the controls (one Dacron, one PTFE), none of which had been used for vascular access. All control grafts were uninfected using the criteria of the absence of bacteria or fungi by culture or microscopy. Sixty-four percent of the cultures from infected grafts were positive and 36% of grafts had bacteria or fungi revealed by microscopy. In Table 5, an overview of the microbiologic assessment is given. When the presence of bacteria was demonstrated by microscopy they were abundant in the outer parts of the graft wall and never seen on the luminal surface (Fig. 4). A total of 10 (28%) of the infected grafts were negative for microorganisms by both of the described methods. Eight or 22% of infected grafts were positive for fungus by culture or microscopy, six of which also had bacterial growth. The different strains grown at culture are listed in Table 6.

**Table 4. Incorporation**

	Scarring perigraft	Scarring in graft wall	Pseudointima
Infected ( <i>n</i> = 36)	27/75%	27/75%	30/83%
Controls ( <i>n</i> = 29)	22/61%	17/47%	13/36%
<i>p</i>	0.3	0.3	0.003

**Table 5.** The presence of microorganisms in the infected grafts was revealed by culture or microscopy alone or in combination

	Culture	Microscopy	Cx/Micro
Bacteria	12	2	4
Fungus	1	–	1
Bact/Fungi	–	1	5
Total	13	3	10

**Fig. 4.** Light microscopy (Gram-stain) of an infected PTFE graft with lots of bacterial clusters (arrows) in the outer half of the graft wall (A = outside graft) but none in the luminal side (=B).

Bacteria were expected to occur in clusters of rounded bodies of equal size. Despite exhaustive electron microscopy, only one possible bacterial cluster was found. Other rounded bodies, easily mistaken for bacteria, were seen but did not fulfill the requirements for classification as bacteria and are derived from fragmentation of other cells like platelets and red blood cells (Fig. 5a, b). There were no layers or other substances that could reasonably be characterised as biofilm. There was no difference in the general appearance at the surface of infected *vs.* control grafts.

### Discussion

The implantation of prosthetic foreign bodies into humans is routine in vascular surgery as well as in many other surgical disciplines. The healing and incorporation of these foreign bodies is a very complex process. Perusal of the literature on biocompatibility underscores the many factors and mechanisms that are involved in foreign body reactions. The basic material itself, additives used during its manufacturing process, porosity, shape, size, movement of the

graft, mechanical fatigue, and location are all factors that have been shown to affect the reaction in, on, and around a foreign body. In addition to activating the coagulation cascade, prosthetic grafts (devices) have also been shown to initiate haemolysis, activate complement as well as leukocytes which in turn release large numbers of highly active proteolytic enzymes.<sup>4-6</sup> Dacron, as used in vascular grafts, has also been shown to decrease the regenerative capacity of arteries.<sup>7</sup> Very recently, even acute allergic reactions with anaphylaxis have been reported after placement of a vascular graft.<sup>8</sup>

The long-term healing response and fibrous incorporation of arterial prostheses in humans is not understood in detail. The basis for our current understanding and use of these devices is the assumption that what has been found in animals is also valid in humans. However, healing responses in different animal species are extremely variable. There are also methodologic questions and problems in how to properly study these reactions. Microscopy of the perigraft tissue and, when applicable, the graft itself seems to be one of the most frequently used and most appropriate methods.<sup>9</sup> Animal studies have shown that after an initial acute inflammatory reaction lasting

**Table 6.** Microorganisms grown at culture of infected vascular grafts

Microorganism	Number
<i>S. aureus</i>	5
<i>Enterococcus</i>	5
<i>Pseudomonas</i>	5
<i>Candida albicans</i>	5
<i>S. epidermidis</i>	4
<i>E. coli</i>	4
<i>Bacteroides fragilis</i>	3
<i>Enterobacter cloacae</i>	3
<i>Serratia marc</i>	2
<i>Xantomonas</i>	1
<i>Proteus</i>	1
<i>Klebsiella pneumoniae</i>	1
<i>Streptococcus viridans</i>	1
<i>Proprii bacteria</i>	1
<i>Torulopsis glabrata</i>	1
Multibacterial	13

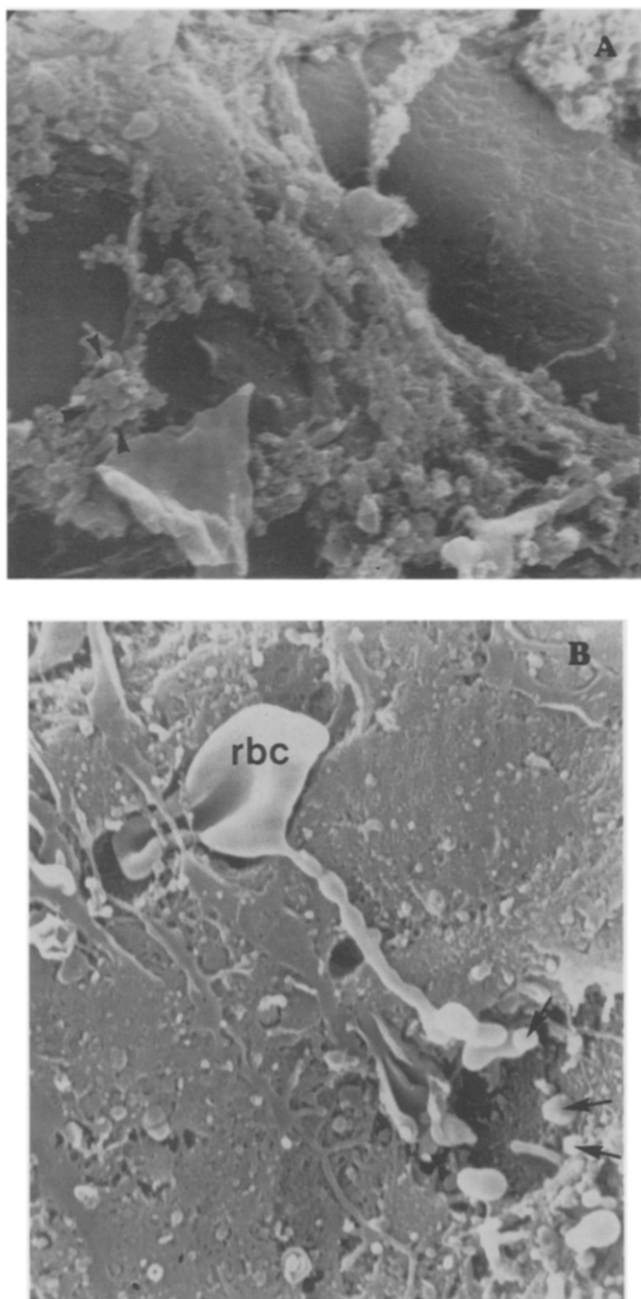


Fig. 5. (a) SEM (magnification 9400) showing a cluster of bacteria (arrows) in the pseudointima of an infected Dacron vascular graft. (b) SEM (magnification 7200) of an infected PTFE graft showing autolysis and fragmentation of a red blood cell (rbc) producing scattered rounded bodies (arrows) that could easily be mistaken for bacteria.

from several days to 1–2 months, a chronic inflammatory reaction emerges. This is associated with fibroblast infiltration of the perigraft space and graft interstices and is of importance for the initial healing process which eventually leads to graft incorporation as the fibrosis matures. The normal timespan for complete graft incorporation in animals has been

estimated to be from a few weeks to 1 year.<sup>4–6</sup> In humans, it has been stated that this process could be completed by 3 months after graft implantation.

Graft complications in humans appear to be related to impaired healing and/or the inflammatory reactions to foreign bodies. For example, orthopedic prostheses are thought to be loosened by chronic inflammation. Sutures in a wound enhance the inflammatory reaction and greatly potentiate the ability of bacteria to produce infection. The present data shows that substantial acute and/or chronic inflammatory reaction exists around most, if not all implanted arterial prosthetic grafts in humans. It can be concluded from many previous studies that a foreign body reaction, like that described here, predisposes to infection.<sup>5,6</sup> Published reports on human vascular grafts and graft related complications first appeared in the 1950s. Graft infections were first described and later reports of possible graft reactions or rejections appeared.<sup>1–3, 10–13</sup> It is possible that at least some of the culture-negative graft infections reported by us and others are really non-infected grafts with surrounding reactions. Dilatation and degradation of Dacron grafts have also been reported and can hypothetically be explained by the effects of tissue and proteolytic enzymes on the prosthetic material.<sup>14</sup>

There is general agreement regarding the clinical significance of chronic vascular graft infection, especially aortic grafts. There is far less agreement regarding the cause of this disastrous complication. These infections are indeed very puzzling considering their very delayed presentation and the relatively high percentage of sterile microbiological cultures obtained from clinically infected specimens. We do not know if the infection is a primary event causing inflammation and separation of the graft from its perigraft capsule or if impaired healing is the primary response with chronic inflammation predisposing to infection. Furthermore, whether the infection starts on the inside of the graft (lumen) or in the perigraft tissue is unknown. Finally, it is uncertain whether or not humans can exert a true host-versus-graft reaction against the most commonly used vascular graft materials (Dacron, PTFE). These issues are all relevant to the present histopathologic data.

Previous reports have described several pathogenic mechanisms for the occurrence of graft infection. Malone *et al.* reported that graft infection is caused by luminal seeding of bacteria in grafts, early after implantation before the development of an intact pseudointima, or late in grafts with incompletely developed pseudointima.<sup>15–17</sup> This concept has been supported by other studies, including well-documented clinical cases.<sup>18</sup> A clinically infected vascular

graft is poorly incorporated within its perigraft capsule and even surrounded by pus or fluid. Yet, as noted earlier, it is not known if the impaired healing is the primary event or if it is secondary to the infection. The incomplete development of pseudointima, a part of the process of incorporation, has also been considered important for the occurrence of graft infections.

No conclusion can be made from our data on the importance of scarring in the perigraft tissue or in the graft wall. The same is true for the pseudointima which was even *better developed* in the infected grafts than in the non-infected control grafts. We found the scarring process to be non-uniform along the graft with a significant and comparable number of grafts in both groups. There was no collagenisation at all despite implantation times of more than 2 years. No significant difference in perigraft fibrosis or pseudointimal development was detected between grafts made of ePTFE or Dacron (we did not distinguish knitted from woven or velour from non-velour grafts). The presence of microorganisms also did not correlate with differences in healing. Consequently, there were culture verified infections in grafts that were well incorporated by currently accepted criteria.

An acute inflammatory reaction and at least some tissue necrosis is expected from a bacterial or fungal infection.<sup>19</sup> However, this was not a consistent finding among the infected grafts. In this study 25% of grafts revealed no histologic signs at all of acute inflammation or necrosis, but this lack of reaction did not correlate with negative microbiological cultures. Possible explanations for these findings could be that the acute inflammation was caused by factors other than microorganisms or that microorganisms might be incapable of exerting their inflammatory provoking actions. Similar findings of culture-positive but histopathologically negative infections have been reported recently in experimental studies by other investigators.<sup>20, 21</sup>

Another interesting feature of the acute inflammatory response was its distribution along the graft and also its cross-sectional distribution in perigraft tissue, graft wall and pseudointima. In some cases the acute inflammation and necrosis were very localised to short segments of the graft with no acute reaction at all on the rest of the graft segments. Together with the uneven distribution of graft healing it is possible, perhaps even probable, that an actual graft infection might be very localized. This could be an important consideration when planning surgical treatment since *partial* graft excision may be feasible.<sup>22</sup> The pre- and intraoperative assessment and determination of the extent of infection is difficult and in some situations

impossible using current criteria and sophisticated technology.

In this study, a strong *chronic inflammatory* response and foreign body reaction was seen in the majority of control as well as infected grafts. It is expected only after the immediate post implantation acute inflammation subsides. It accompanies the initial incorporation process and includes fibroblast infiltration of the graft. We found this chronic reaction persisted even in chronically implanted grafts. A strong chronic inflammatory response occurring several years after graft implantation may be considered "normal" or serve as a marker of incomplete incorporation. We believe that the significant T-lymphocyte population seen in half of infected and control grafts is strong support for a true host versus graft reaction.

The proposed concept that primary graft infection results from bacterial seeding of the luminal surface of the graft from the blood stream deserves close scrutiny. The many possible sources of blood-borne bacteria include peripheral wounds with lymphatic transport of bacteria, bacterial infection of the arterial wall itself or temporary bacteremias after surgical instrumentation and examination. There are known to be variations in luminal covering by pseudointima and the capability of the most commonly encountered microorganisms (*S. aureus* and *S. epidermidis*) to adhere to exposed foreign surfaces.<sup>23-26</sup> However, a recent well designed experimental study in dogs showed that the primary site of infection was the perigraft tissue, with secondary invasion of the graft wall and *finally* the luminal lining.<sup>27</sup> Our findings strongly indicate that this is also true in humans. The distribution of microorganisms found at microscopy was always abundant in the perigraft tissue but scant or absent on the luminal side. Furthermore, experimental studies have clearly shown that when grafts are infected from the luminal surface, this is accompanied as expected by an acute inflammatory reaction in the affected part of the graft.<sup>20</sup> In our series of human specimens, the acute inflammation was always (disregarding the presence or absence of microorganisms), most significant on the external surface of the graft in the perigraft tissue. It was less evident within the graft wall and was absent or very rare on the luminal surface.

Some bacterial strains are known to produce a slime layer in culture. For example, *in vitro* some strains of *S. epidermidis* can envelop themselves in a "biofilm" of an amorphous exopolysaccharide protecting them from the host defence mechanisms as well as from antibiotics.<sup>28, 29</sup> Electron microscopic support for this type of biofilm has been presented in humans

with infections of arterial lines and pacemaker electrodes.<sup>30, 31</sup> Experimental models of vascular graft infection using infusion of slime-producing bacteria have shown that in this particular setting, the biofilm is of importance for the development of infection.<sup>32-34</sup> This concept is also very attractive in explaining some of the clinical characteristics of human prosthetic vascular graft infections (chronicity, late onset of appearance, type of bacteria involved, etc.) but is of course relevant only regarding infections by slime-producing bacteria. Direct evidence for the presence of biofilm in human vascular graft infection has, however, not been presented yet. The fact that ultrasonication of explanted grafts gives a higher yield of positive cultures and that bacteria picked up from infected grafts *in vitro* can produce slime only gives indirect support for this concept.<sup>32-35</sup> Our expectations were to find slime layers or bacteria adhering to the luminal surfaces of the human explanted vascular grafts as previously reported in clinical and experimental studies. Despite extensive SEM only one possible bacterial cluster was found in one of the infected grafts. This, however, is in accordance with the cross-sectional distribution of microorganisms found by light microscopy. Consequently, our results do not provide the final evidence for the presence of biofilm in human vascular graft infection. This should be compared to previous studies reporting on what is termed "biofilm infections" in as many as 90% of pseudoaneurysms and 69% of thrombosed grafts.<sup>36</sup> This very high yield of bacteria, in thrombosed grafts in particular, raises two questions; are these biofilm infections (=infections with *Staphylococcus epidermidis* requiring ultrasonication to dislodge bacteria to grow in culture media) a very common type of contamination of implanted grafts with limited importance in chronic graft infection; are biofilm infections of importance in graft thrombosis?

In conclusion, this study shows that what we clinically define as a vascular graft infection, has histologic characteristics that are similar to non-infected grafts. These infections seem to be related to a strong chronic inflammatory reaction and foreign body reaction as well as a true host *vs.* graft reaction. Furthermore, by showing that vascular graft infections in humans seem to have their nidus in the perigraft tissue, it casts some doubt on what has been found in experimental studies regarding the etiology of this condition.

Our study also raises several questions regarding the human tolerance for vascular graft material. What is the true histopathologic healing response in humans? Are there individual variations in this healing response? Are grafts merely tolerated by

individuals with a dynamic host *vs.* graft response? Can graft material be altered to achieve even better healing than they do today? Can the external graft environment be altered to allow healing of contaminated yet retained prostheses? The answers to these questions may allow further progress in the prevention and more effective treatment of this dreaded surgical complication of arterial repair.

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